REMARKS

The amendments set out above and the following remarks are believed responsive to the points raised by the Office Action dated July 8, 2002.

Information Disclosure Statement

An Information Disclosure Statement, including a Form PTO-1449, and copies of the 107 documents listed on the Form, was submitted on October 8, 2002, along with the appropriate fee. It is respectfully requested that the Examiner place his initials in the appropriate area of the Form, thereby indicating his consideration of the documents, and return the initialed Form to Applicants.

Discussion of Specification and Claim Amendments

The specification has been amended to correct minor grammatical and typographical errors. Claims 50 and 73 have been amended to further sharpen the claim language and claim 96 has been added and is directed to an embodiment of the invention. The basis for the amended claim language may be found within the original specification, claims and drawings. No new matter has been added.

The Office Action

The Office Action sets forth the following grounds for rejection: (1) claims 50-95 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 5,976,577 (Green et al.).

The Present Invention

The present invention is directed to a process for the preparation of a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation and/or agglomeration or particle size growth. Claims 50-96 are currently pending. A set of pending claims is attached.

Discussion of Obviousness Rejection

Claims 50-95 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Green et al. The Office Action contends Green et al. discloses essential elements of the claimed invention and that it would have been obvious to one of ordinary skill in the art to vary the

particle sizes taught by Green et al. with the expectation of obtaining the desired dissolution rates. This rejection is respectfully traversed.

The Office Action has failed to make a *prima facie* case for obviousness. Green et al. fails to disclose or suggest the presently claimed invention. For example, Green et al. fails to disclose a process for the preparation of a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation and/or particle agglomeration or particle size growth. Green et al. also fails to disclose a process including forming an admixture containing a stable aqueous homogenous suspension having a particle size of about 10 μm or less. Further, Green et al. does not disclose a process including producing a solidified suspension of surface stabilized particles dispersed and embedded throughout a support matrix, wherein said matrix dissolves or substantially disperses in a rapid disintegration time when in contact with an aqueous environment to release said surface stabilized primary particles into said aqueous environment as a suspension without irreversible particle aggregation and/or particle agglomeration and without particle size growth.

Green et al. is directed to a process for preparing rapidly dispersing solid oral dosage forms using coarse coated drug particles (i.e., coarse particles having a size up to 1 millimeter, for example 75 to 400 μm) (see Green et al., column 2, lines 48-49 and column 3, lines 15-18). Nothing in Green et al. would lead one skilled in the art to utilize particles having a particle size of about 10 μm or less as in the presently claimed invention. Indeed, Green teaches directly away from using smaller particle sizes. For example, at column 3, lines 6-15, Green et al. teaches,

> "Size of the particles has an important effect on the rate of release of drug when coated. A smaller particle has a much larger overall surface area for diffusion. As a result, the rate of release of drug is greater the smaller the particle. Current coating techniques are able to effectively coat particles greater than 100 μm, whereas particles less than 100 μm may not have an intact coat, which will result in rapid release of the drug once in suspension. Coating of larger particles therefore decreases the rate of release of drug."

Further, the presently claimed invention includes an unexpected and superior property, i.e., a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation and/or particle agglomeration or particle size growth. In the presently claimed invention, in contrast to Green et al., nearly the same particle size dispersion was obtained after lyophilization and resuspension as before lyophilization. For example, as shown in the Declaration by Awadhesh Mishra submitted August 14, 2001 ("the Declaration"),

the product prepared according to Green et al., containing particles greater than 10 μm, exhibited substantial particle growth when placed in contact with an aqueous environment. In contrast, as seen in the Declaration, the present inventive process yielded a suspension which does not exhibit particle growth when placed in contact with an aqueous environment. As seen in Figures 1 and 2 of the Declaration, the product prepared according to the process of Green included a suspension having particle sizes of up to 48.27 μm before lyophilization, and a suspension having particle sizes of up to 301.68 μm after lyophilization and rehydration. However, the product prepared according to the present inventive process, yielded a suspension having particles sizes of 2.28 μm or less before lyophilization, which did not increase after lyophilization, still yielding particles sizes of 2.28 μm or less after lyophilization.

Clearly, Green et al. does not disclose or even suggest a process for the preparation of a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation and/or particle agglomeration or particle size growth.

In view of the foregoing, claims 50-96 are patentable over Green et al.

Conclusion

The application is considered in good and proper form for allowance. Should there remain any issues outstanding, the Examiner is invited to call the undersigned at her Washington, D.C. office.

Respectfully submitted,

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Date: December 9, 2002
SDS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

PARIKH et al.

Application No. 09/443,863 Art Unit: 1615

Filed: November 19, 1999 Examiner: G. Kishore

For: DISPERSIBLE PHOSPHOLIPID STABILIZED MICROPARTICLES

AMENDMENTS TO SPECIFICATION AND CLAIMS MADE IN RESPONSE TO OFFICE ACTION DATED JULY 8, 2002

Amendments to the paragraph beginning at page 3, line 24:

This invention is directed to an improvement in the dispersibility of micronized particles through the specific selection of excipients and methodology necessary to recover the primary particles. Inherent in this approach is the ability to produce stable aqueous suspensions of micron or submicron sized particles of water insoluble or poorly water-soluble compounds. These particles, which are required in the practice of the present invention, can be prepared according to the methods disclosed in U.S. Pat. No. 5,091,187 and 5,091,188 as well as WO 98/07414, whose disclosure is incorporated by reference. Briefly, water insoluble or poorly soluble compounds are dispersed in an aqueous medium in the presence of surface modifying agents or combinations of agents of which at least one is a phospholipid adsorbed on the surface thereof. Particle fragmentation occurs when the aforementioned suspension is subjected to stress as a result of processing with the use of various methods known in the art including, but not limited to, sonication, milling, homogenization, microfluidization, and antisolvent and solvent precipitation. The particle so produced is referred to as a microparticle which is defined herein as a solid particle of irregular, non-spherical or spherical shape having a nominal diameter of from nanometers to micrometers on to which is adsorbed ~~a~~ at least one surface modifying agent of which one is a phospholipid.

Amendments to the paragraph beginning at page 6, line 29:

The resulting homogeneous suspension of microparticles stabilized by one or more surface modifiers is then mixed with matrix-forming bulking and/or releasing agents (dry or as an aqueous solution) and is then dried. The bulking or matrix-forming agent provides a mass in which the particles or drug are embedded or ~~retain~~ retained. The release agent assists in disintegration of the matrix when it contacts aqueous media. The bulking/releasing agents are chosen in order to produce a support matrix that, upon drying, will yield rapidly dispersible tablets that release the primary particles upon reconstitution in an aqueous medium. Examples of matrix-forming/release agents include (a) saccharides and polysaccharides such as mannitol, trehalose, lactose, sucrose, sorbitol, maltose; (b) humectants such as glycerol, propylene glycol, polyethylene glycol; (c) natural or synthetic polymers such as gelatin, dextran, starches, polyvinylpyrrolidone, poloxamers, acrylates, (d) inorganic additives such as microcrystalline cellulose, hydroxymethyl cellulose, hydroxypropyl cellulose, methylcelluloses. Matrix forming agents may be added prior to producing the micronized particles of the therapeutic agent (formulation) or to the homogeneous suspension of microparticles prior to freeze-drying. The concentration of the matrix forming agents in the aqueous suspension can very between 0.1% w/w and 90% w/w, preferably between 0.5% w/w and more preferably between 1% w/w and 20% w/w.

Amendments to existing claims:

50. (Amended) A process for the preparation of a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation and/or particle agglomeration or particle growth comprising ~~the steps of~~:

a) forming an admixture of a stable aqueous homogenous suspension of micronized surface stabilized primary particles of a water-insoluble or poorly water-soluble drug with a matrix-forming bulking/releasing agent or a mixture of matrix-forming bulking and releasing agents, wherein said stable aqueous primary particle suspension has ~~dispersity with~~ a ~~volume weighted mean~~ particle size ~~from 0.2 micrometers to 5 micrometers~~ of about 10 μm or less, each primary particle is a solid drug particle on to which is adsorbed at least one surface modifying agent of which one is a phospholipid, ~~said matrix-forming agent or agents are present in an amount sufficient to allow drying of said admixture to a solidified suspension without irreversible particle aggregation and/or particle agglomeration or particle growth~~; ~~then,~~

b) drying said admixture to produce a solidified suspension of said surface stabilized primary particles dispersed and embedded throughout a support matrix of said matrix-forming agent or agents, wherein said matrix dissolves or substantially disperses in a rapid disintegration time when in contact with an aqueous environment to release said surface stabilized primary particles into said aqueous environment as a suspension without irreversible particle aggregation and/or particle agglomeration and without particle size growth; ~~then,~~

c) optionally course milling and blending said solidified suspension with one or more pharmaceutically acceptable excipients to provide a dried powder; and ~~then,~~

d) forming said dried material or said dried powder into a solid dosage form.

73. (Amended) A process for the preparation of a rapidly disintegrating solid dosage form capable of forming a stable suspension without irreversible particle aggregation and/or particle agglomeration or particle growth comprising ~~the steps of~~:

a) forming an admixture of a stable aqueous homogenous suspension of micronized surface stabilized primary particles of a water-insoluble or poorly water-soluble drug with a matrix-forming bulking/releasing agent or a mixture of matrix-forming bulking and releasing agents, wherein said stable aqueous primary particle suspension has ~~dispersity with~~ a ~~volume weighted mean~~ particle size ~~from 0.2 micrometers to 5 micrometers~~ of about 10 μm or less, each primary particle is a solid drug particle on to which is adsorbed at least one surface modifying agent of which one is a phospholipid~~, said matrix-forming agent or agent present in an amount sufficient to allow drying of said admixture without irreversible particle aggregation and/or particle agglomeration or particle growth; then,~~;

b) distributing the admixture of ~~step~~ (a) into unit dosage form molds; and ~~then,~~

c) freeze-drying said admixture in said unit dosage form molds to produce a solidified suspension of said surface stabilized primary particles dispersed and embedded throughout a support matrix of said matrix-forming agent or agents, wherein said matrix dissolves or substantially disperses in a rapid disintegration time when in contact with an aqueous environment to release said surface stabilized primary particles into said aqueous environment as a suspension without irreversible particle aggregation and/or particle agglomeration and without particle size growth.